LINFOMA FOLLICOLARE

Dalla parte della terapia con CAR-T nella malattia recidivata

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Disclosures of Annalisa Chiappella

Company name	Advisory board	Lecture fees/Educational Events
Abbvie	x	
Incyte	x	
Gilead-Sciences/Kite Pharma Inc.	x	x
Sobi	x	
Eli Lilly		x

R/R B-NHL: CD19-targeting CAR T-cell therapies in Italy

	Indications
Axicabtagene ciloleucel	▪ **R/R LBCL** after ≥2 lines of systemic tx, including DLBCL NOS, t-FL, FL3B, HGBCL, **PMBCL** ▪ **LBCL (excluded PMBCL)** that is refractory to/relapsed within 12 mo of 1L CIT ▪ **R/R FL** after ≥3 lines of therapy
Brexucabtagene autoleucel	▪ **R/R MCL** after ≥2 lines of systemic therapies
Lisocabtagene maraleucel	▪ **R/R LBCL** after ≥2 lines of systemic tx, including DLBCL NOS, t-iNHL, FL3B, HGBCL, **PMBCL** ▪ **LBCL (included PMBCL)** that is refractory to/relapsed within 12 mo of 1L CIT ★ ▪ **R/R FL** who have received ≥2 prior lines of systemic tx* COMING SOON
Tisagenlecleucel	▪ **R/R LBCL (excluded PMBCL)** after ≥2 lines of systemic tx ▪ **R/R FL** after ≥2 lines of tx

Pivotal Anti-CD19 CAR T-Cell Therapy Trials in R/R FL

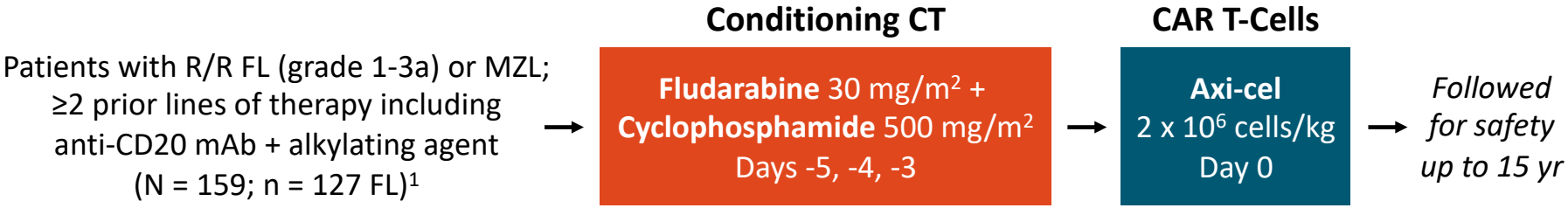
Outcome	Phase II ZUMA-5[1,2]	Phase II ELARA[3,4]	Phase II TRANSCEND WORLD[5]	Phase II TRANSCEND-FL[6]
CAR T-cell agent	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel	Lisocabtagene maraleucel
Patient population	R/R FL	R/R FL	R/R tFL and FL3B	R/R FL
Patients pheresed/treated, n	127/124	98/97	14/10‡	139/130
Bridging therapy, %	3	--	100	38
ORR, %	94*	86	70	97
▪ CR	79*	69	50	94
Survival	mPFS: 40.2 mo* 36-mo OS: 76%*	mPFS: 29.5 mo mOS: NE	mPFS: 6.3 mo mOS: 14.7 mo	12-mo PFS: 83% 12-mo OS: 93%
CRS (grade ≥3), %	7†	0	0	1
Neurotoxicity (grade ≥3), %	19†	3	0	2
Tocilizumab, %	50†	--	30	14

*Includes 127 evaluable patients with FL. †Includes 84 with FL and 20 with MZL. ‡Includes 3 patients with tFL and 1 patient with FL3B.

1. Jacobson. Lancet Oncol. 2022;23:91. 2. Neelapu. Blood. 2024;142:496. 3. Thieblemont. ASH 2021. Abstr 131.
4. Fowler. Nat Med. 2022;28:325. 5. Makita. Cancer Med. 2022;11:4889. 6. Morschhauser. Nat Med. 2024;30:2199.

ZUMA-5: Axicabtagene Ciloleucel in R/R FL and MZL

- Multicenter, single-arm phase II trial[1,2]



Patients with SD but no relapse >1 yr from completion of last therapy ineligible. Single-agent anti-CD20 mAb not counted as line of therapy for eligibility. Median time to delivery of axi-cel: 17 days following leukapheresis.

- **Primary endpoint:** ORR (CR and PR) by IRC per Lugano classification
  - In primary analysis, ORR was 94% for 84 patients with FL after 17.5 mo follow-up[2]
- **Key secondary endpoints:** CR rate (IRRC assessed), ORR (investigator assessed), DoR, PFS, OS, AEs, CAR T-cell and cytokine levels

Neelapu, ASH 2022; Jacobson, Lancet 2022.

Five-Year Follow-Up Analysis of ZUMA-5: Axicabtagene Ciloleucel in Relapsed/Refractory Indolent Non-Hodgkin Lymphoma

Sattva S. Neelapu, MD[1]; Julio C. Chavez, MD[2]; Alison R. Sehgal, MD[3]; Narendranath Epperla, MD, MS[4]; Matthew L. Ulrickson, MD[5]; Emmanuel Bachy, MD, PhD[6]; Pashna N. Munshi, MD[7]; Carla Casulo, MD[8]; David G. Maloney, MD, PhD[9]; Sven de Vos, MD, PhD[10]; Ran Reshef, MD[11]; Lori A. Leslie, MD[12]; Olalekan O. Oluwole, MD, MPH, MBBS[13]; Ibrahim Yakoub-Agha, MD, PhD[14]; Rashmi Khanal, MD[15]; Joseph D. Rosenblatt, MD[16]; Jacob Wulff, DrPh[17]; Rhine R. Shen, PhD[17]; Wangshu Zhang, PhD[17]; Soumya Poddar, PhD[17]; Harry Miao, MD, PhD[17]; Olga Nikolajeva, MD[17]; and Caron A. Jacobson, MD[18]

J Clin Oncol 43:3573-3577

TABLE 1. Baseline Characteristics of Enrolled Patients

Characteristic	FL (n = 127)	MZL (n = 31)	All Patients (N = 159)[a]
Age, years, median (range)	60 (34-79)	64 (43-77)	60 (34-79)
≥65 years, No. (%)	40 (31)	14 (45)	54 (34)
Male sex, No. (%)	75 (59)	15 (48)	90 (57)
ECOG PS 1, No. (%)	48 (38)	16 (52)	65 (41)
Stages III-IV disease, No. (%)	109 (86)	29 (94)	139 (87)
High-risk FLIPI (≥3), No. (%)	56 (44)	—	—
High tumor bulk (GELF criteria), No. (%)[b]	65 (51)	16 (52)	82 (52)
Prior therapies, No., median (range)[c]	3 (1-10)	3 (2-8)	3 (1-10)
≥3 prior lines of therapy, No. (%)	80 (63)	20 (65)	101 (64)
R/R subgroup, No. (%)			
Refractory to last prior therapy	87 (69)	25 (81)	113 (71)
POD24 from initiating first anti-CD20 mAb–containing therapy[d]	70 (56)	18 (60)	89 (57)
Lymphoma present in bone marrow, No. (%)[e]	35 (28)	14 (45)	49 (31)

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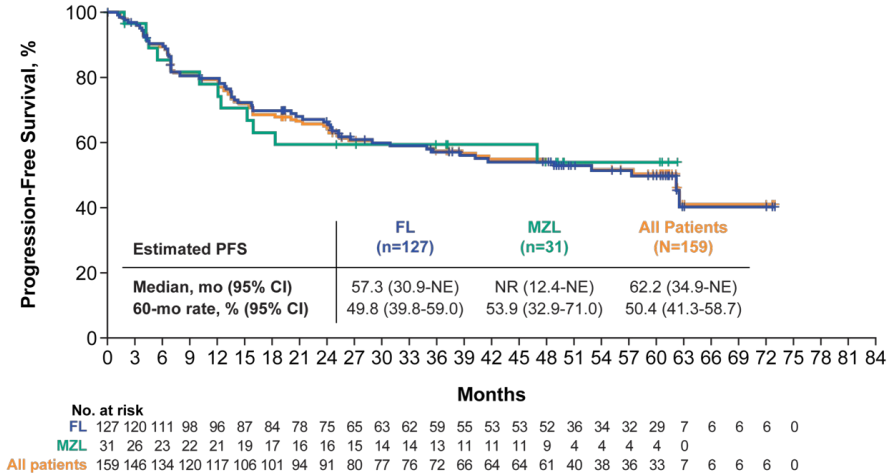
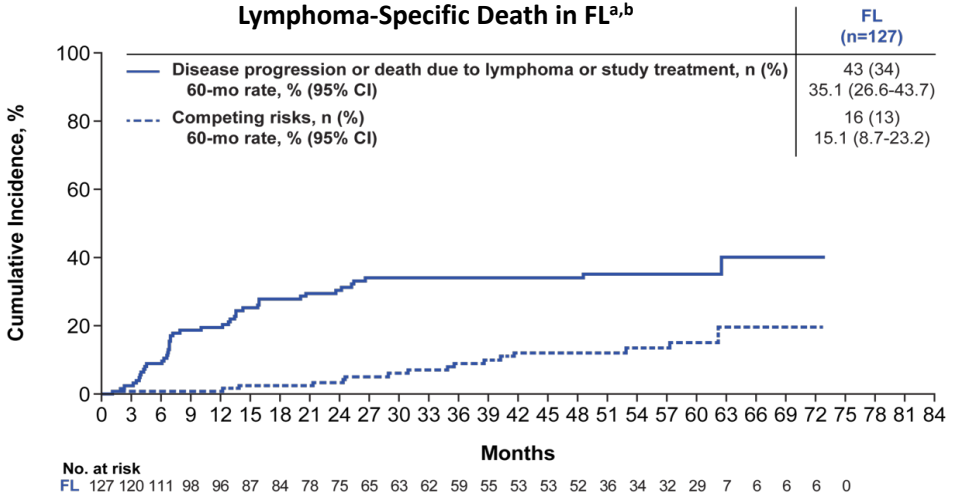
Progression-Free Survival[a]



Cumulative Incidence of Progression and Lymphoma-Specific Death in FL[a,b]



Median follow-up of 64.6 months

- Median PFS was 62.2 months; the 60-month PFS rate was 50.4%
  - 60-month PFS rates in patients with FL were consistent regardless of high-risk factors, including POD24
  - In those with a CR, the 60-month PFS rate was 61.9%; in those with PR, the rate was 9.1%
- Among patients with FL, the 60-month rate of progression or lymphoma-specific death was 35.1%

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TABLE 2. Summary of Total Deaths per Year by Category

Category	All Patients (N = 159), No. (%)	Years Post–Axi-Cel Infusion, No. (%)					
		0-1	1-2	2-3	3-4	4-5	>5
Patients who died	46 (30)	10 (7)	15 (10)	11 (7)	6 (4)	3 (2)	1 (1)
Primary cause of death							
Relapse mortality							
Progressive disease	14 (9)	5 (3)	5 (3)	2 (1)	1 (1)	1 (1)	0
Non-PD death after PD[a]	9 (6)	1 (1)	3 (2)	4 (3)	1 (1)	0	0
Nonrelapse mortality							
Second primary malignancy[b]	6 (4)	1 (1)	2 (1)	1 (1)	2 (1)	0	0
Cardiac related	3 (2)	0	1 (1)	0	1 (1)	0	1 (1)
Infection related	11 (7)	2 (1)	2 (1)	4 (3)	1 (1)	2 (1)	0
Other	3 (2)	1 (1)	2 (1)	0	0	0	0

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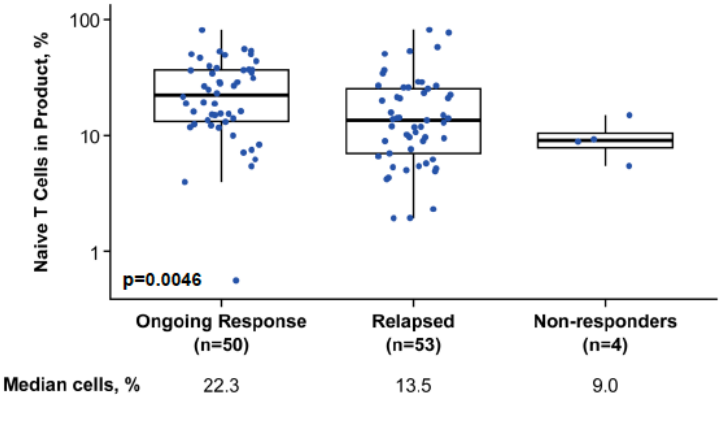
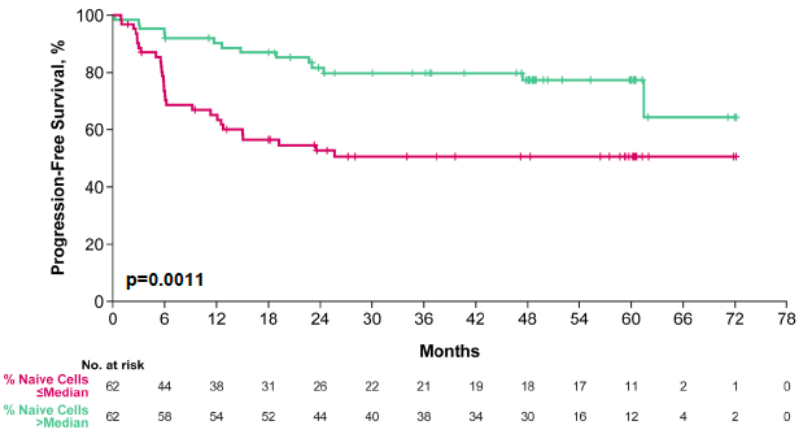
Naive T Cells in Product



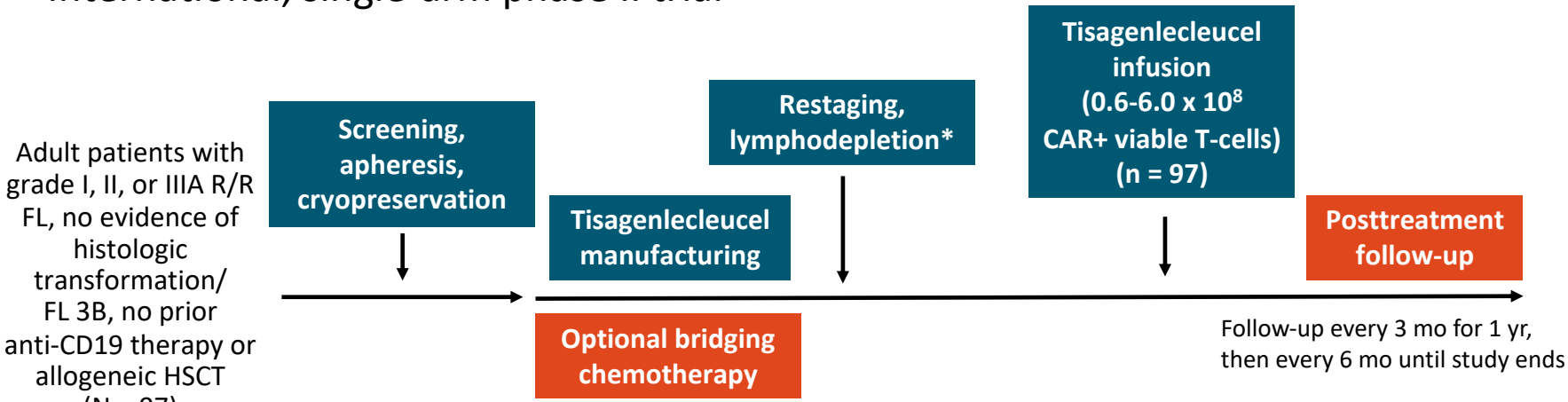
PFS by Median Naive T Cells in Product



- Among patients with FL, a higher percentage of naive T cells (CCR7+CD45RA+) in axi-cel product, indicative of naive phenotype, was associated with ongoing response at 60 months and longer PFS

ELARA: Tisagenlecleucel in R/R FL

- International, single-arm phase II trial



*Lymphodepleting therapy: fludarabine 25 mg/m^2/day IV for 3 days + cyclophosphamide 250 mg/m^2/day IV for 3 days or bendamustine 90 mg/m^2/day IV for 2 days.

- **Primary endpoint:** CRR by IRC
- **Secondary endpoints:** ORR, DoR, PFS, OS, safety, cellular kinetics

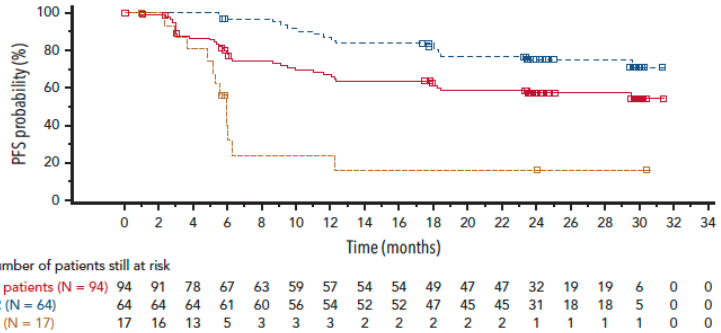
Fowler, Nat Med 2022.

Durable response after tisagenlecleucel in adults with relapsed/refractory follicular lymphoma: ELARA trial update

blood® 25 APRIL 2024 | VOLUME 143, NUMBER 17

Martin Dreyling,[1] Nathan Hale Fowler,[2,3] Michael Dickinson,[4] Joaquin Martinez-Lopez,[5] Ame Kolstad,[6] Jason Butler,[7] Monalisa Ghosh,[8] Leslie Popplewell,[9] Julio C. Chavez,[10] Emmanuel Bachy,[11] Koji Kato,[12] Hideo Harigae,[13] Marie José Kersten,[14] Charalambos Andreadis,[15] Peter A. Riedell,[16] P. Joy Ho,[17] José Antonio Pérez-Simón,[18] Andy I. Chen,[19] Loretta J. Nastoupil,[20] Bastian von Tresckow,[21,22] Andrés José María Ferreri,[23] Takanori Teshima,[24] Piers E. M. Patten,[25,26] Joseph P. McGuirk,[27] Andreas L. Petzer,[28] Fritz Offner,[29] Andreas Viardot,[30] Pier Luigi Zinzani,[31,32] Ram Malladi,[33] Ines Paule,[34] Aiesha Zia,[34] Rakesh Awasthi,[35] Xia Han,[36] Davide Germano,[34] Darragh O'Donovan,[37] Roberto Ramos,[36] Harald J. Maier,[34] Aisha Masood,[36] Catherine Thieblemont,[38] and Stephen J. Schuster[39]

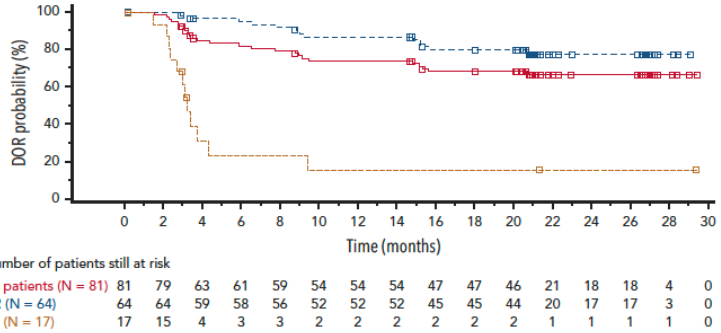
A



PFS Probability	% (95% CI)
12 months, all patients	67.2 (56.3-75.9)
24 months, all patients	57.4 (46.2-67.0)
12 months, patients in CR	87.2 (76.0-93.4)
24 months, patients in CR	75.3 (62.4-84.3)

Kaplan-Meier medians
All patients: NE months, 95% CI [18.2-NE]
CR: NE months, 95% CI [NE-NE]
PR: 5.9 months, 95% CI [4.9-6.3]

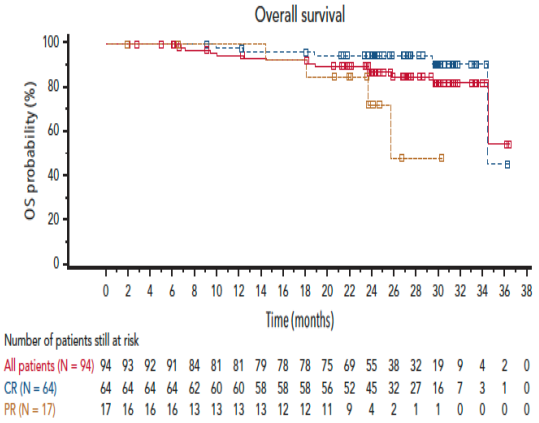
B



DOR Probability	% (95% CI)
12 months, all patients	73.8 (62.4-82.3)
24 months, all patients	66.4 (54.3-76.0)
12 months, patients in CR	86.9 (75.6-93.2)
24 months, patients in CR	77.8 (64.7-86.5)

Kaplan-Meier medians
All patients: NE months, 95% CI [NE-NE]
CR: NE months, 95% CI [NE-NE]
PR: 3.2 months, 95% CI [2.3-4.3]

C



OS Probability	% (95% CI)
12 months, all patients	95.3 (88.1-98.2)
24 months, all patients	87.7 (78.3-93.2)
12 months, patients in CR	98.4 (88.9-99.8)
24 months, patients in CR	95.0 (85.3-98.4)

Kaplan-Meier medians
All patients: NE months, 95% CI [34.5-NE]
CR: 34.5 months, 95% CI [34.5-NE]
PR: 25.8 months, 95% CI [23.7-NE]

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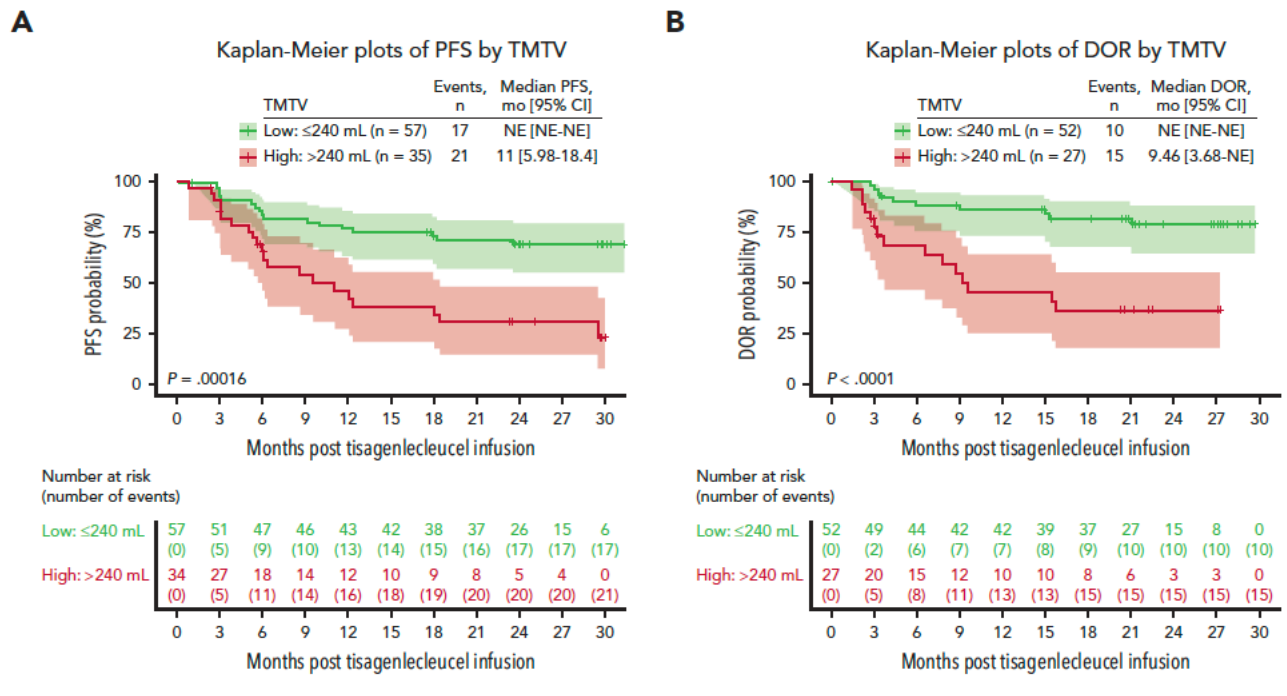

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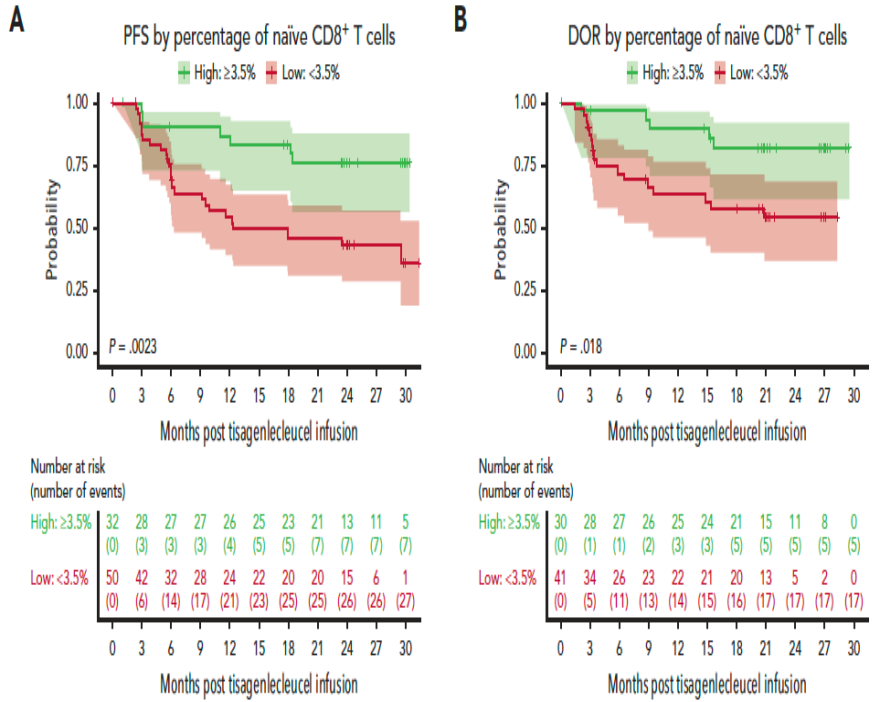
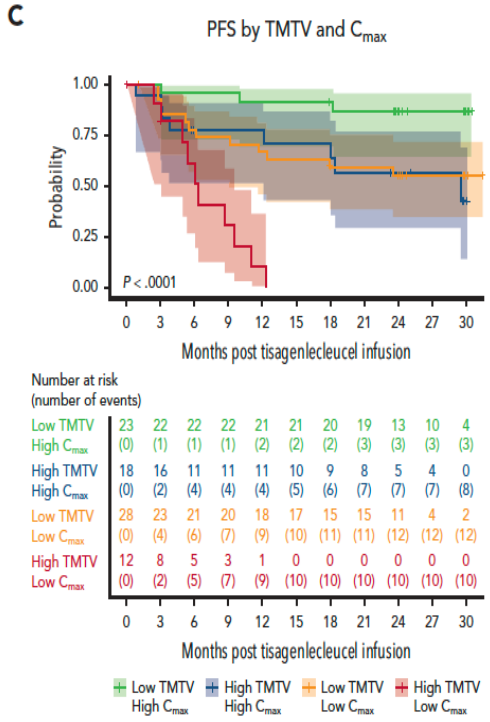
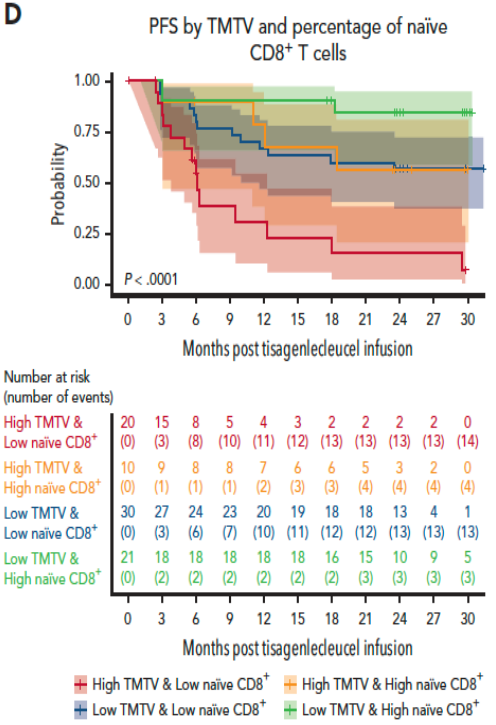
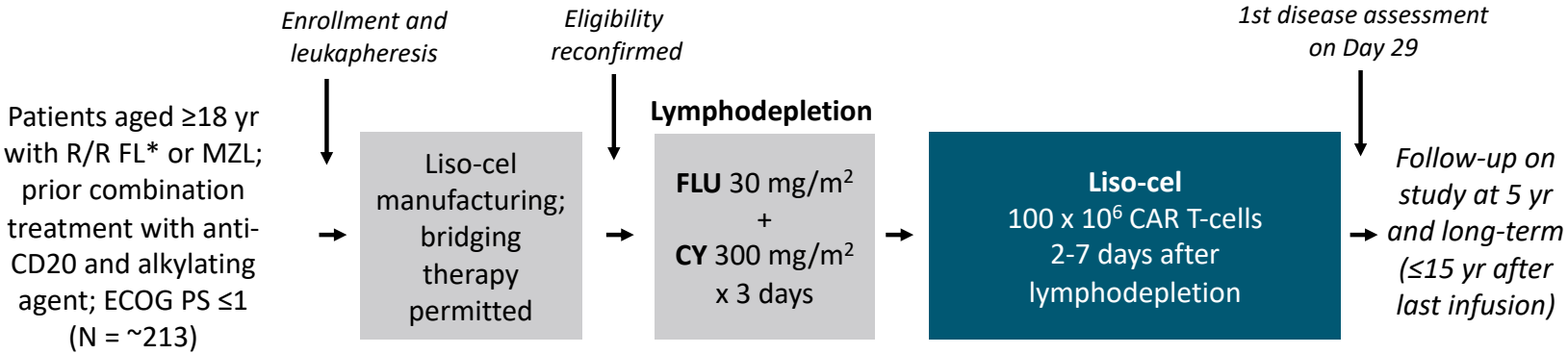






TRANSCEND FL: Lisocabtagene maraleucel in R/R FL and MZL

- Multicenter, open-label, single-arm, phase II trial; data cutoff January 27, 2023



*High-risk features required for 2L patients: POD24 (progression ≤24 mo of diagnosis and after anti-CD20/alkylating agent therapy within 6 mo) or ≥1 mGELF criteria (FL-related symptoms, threatened end-organ function, cytopenia that is secondary to lymphoma or bulky disease, splenomegaly, or stable progression over ≥6 mo).

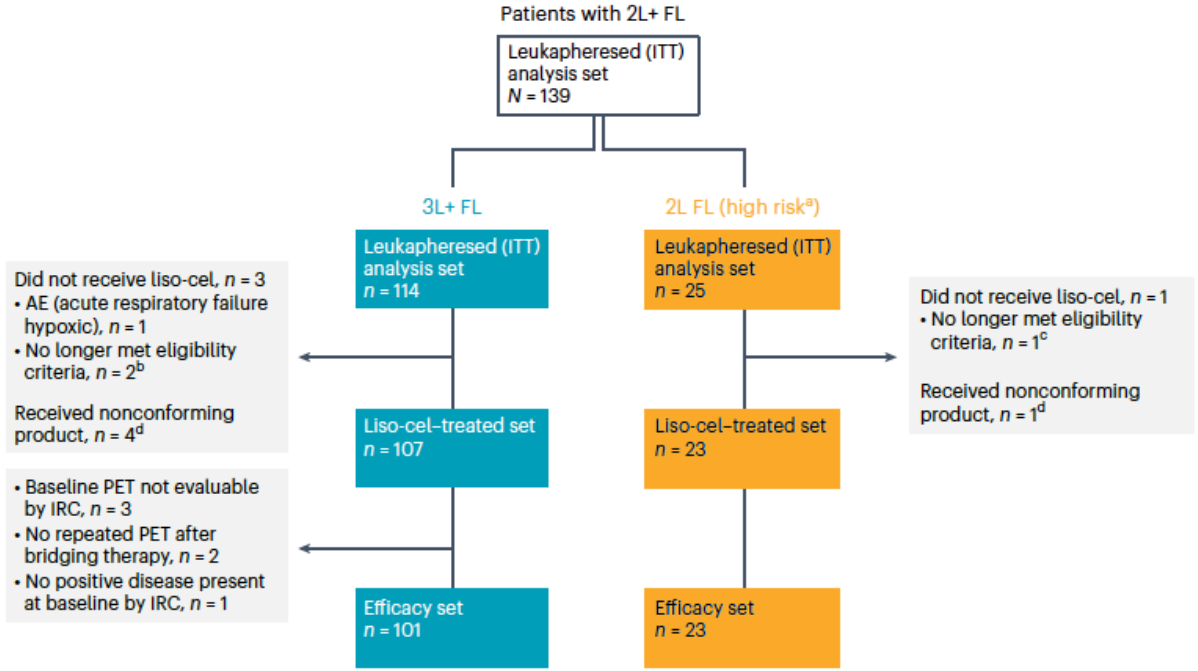
- **Primary endpoint**: IRC-assessed ORR via PET/CT (Lugano 2014 criteria)
- **Key secondary endpoints**: CRR, DoR, CR DoR, PFS, OS, safety

Morschhauser, ASH 2023.

Lisocabtagene maraleucel in follicular lymphoma: the phase 2 TRANSCEND FL study

Nature Medicine | Volume 30 | August 2024 | 2199–2207

Franck Morschhauser[1], Saurabh Dahiya[2,3], M. Lia Palomba[4], Alejandro Martin Garcia-Sancho[5], Juan Luis Reguera Ortega[6], John Kuruvilla[7], Ulrich Jäger[8], Guillaume Cartron[9], Koji Izutsu[10], Martin Dreyling[11], Brad Kahl[12], Hervé Ghesquieres[13], Kirit Ardeshna[14], Hideki Goto[15], Anna Maria Barbui[16], Jeremy S. Abramson[17], Peter Borchmann[18], Isabelle Fleury[19], Stephan Mielke[20], Alan Skarbnik[21], Sven de Vos[22], Manali Kamdar[23], Reem Karmali[24], Andreas Viardot[25], Thalia Farazi[26], Omotayo Fasan[27], James Lymp[28], Min Vedal[28], Rina Nishii[27], Ariel Avilion[28], Jessica Papuga[29], Jinender Kumar[27] & Loretta J. Nastoupil[30]



Lisocabtagene maraleucel in follicular lymphoma: the phase 2 TRANSCEND FL study

Nature Medicine | Volume 30 | August 2024 | 2199–2207

	3L+ FL (*n*=107)	2L FL (*n*=23)	2L+ FL (*n*=130)
Median age (range), years	62 (23–80)	53 (34–69)	60 (23–80)
FLIPI at screening, *n* (%)			
Low risk (0–1)	12 (11)	11 (48)	23 (18)
Intermediate risk (2)	34 (32)	4 (17)	38 (29)
High risk (3–5)	61 (57)	8 (35)	69 (53)
SPD ≥ 50 cm^2 before LDC per IRC, *n* (%)	22 (21)	3 (13)	25 (19)
LDH > ULN before LDC, *n* (%)	47 (44)	6 (26)	53 (41)
mGELF criteria met at time of most recent relapse, *n* (%)	57 (53)	16 (70)	73 (56)
Median prior lines of systemic therapy (range)	3 (2–10)	1 (1–1)	2 (1–10)
Prior HSCT[c], *n* (%)	33 (31)	0	33 (25)
Received prior rituximab and lenalidomide, *n* (%)	23 (21)	0	23 (18)
Prior bendamustine, *n* (%)			
No prior bendamustine	42 (39)	17 (74)	59 (45)
Prior bendamustine ≤6 months before leukapheresis	4 (4)	1 (4)	5 (4)
Prior bendamustine >6 months and ≤12 months before leukapheresis	4 (4)	2 (9)	6 (5)
Prior bendamustine >12 months before leukapheresis	57 (53)	3 (13)	60 (46)
Refractory to systemic therapy[d], *n* (%)	38 (36)	3 (13)	41 (32)
PD while on the last LOT or ≤6 months of completing the last LOT, *n* (%)	69 (64)	15 (65)	84 (65)
POD24 from diagnosis[e], *n* (%)	46 (43)	12 (52)	58 (45)
FL progression ≤24 months of first-line therapy with anti-CD20 antibody and alkylator, *n* (%)	58 (54)	15 (65)	73 (56)
Double refractory (anti-CD20 + alkylator)[f], *n* (%)	69 (64)	11 (48)	80 (62)
Median time-to-event analyses (range)			
Diagnosis to first PD, years	2.0 (0.25–16.5)	1.8 (0.5–11.2)	2.0 (0.25–16.5)
Initial treatment to first PD, years	1.5 (0.1–8.8)	1.4 (0.3–11.1)	1.5 (0.1–11.1)
Completion of last LOT to SD or PD[g], years	0.15 (0–9.6)	0.3 (0–8.8)	0.15 (0–9.6)
Diagnosis to liso-cel infusion, years	5.1 (0.7–35.3)	2.0 (0.8–11.4)	4.7 (0.7–35.3)
Most recent relapse to liso-cel infusion, years	0.4 (0–3.2)	0.3 (0.1–1.3)	0.3 (0–3.2)
Received bridging therapy, *n* (%)	44 (41)	5 (22)	49 (38)

Lisocabtagene maraleucel in follicular lymphoma: the phase 2 TRANSCEND FL study

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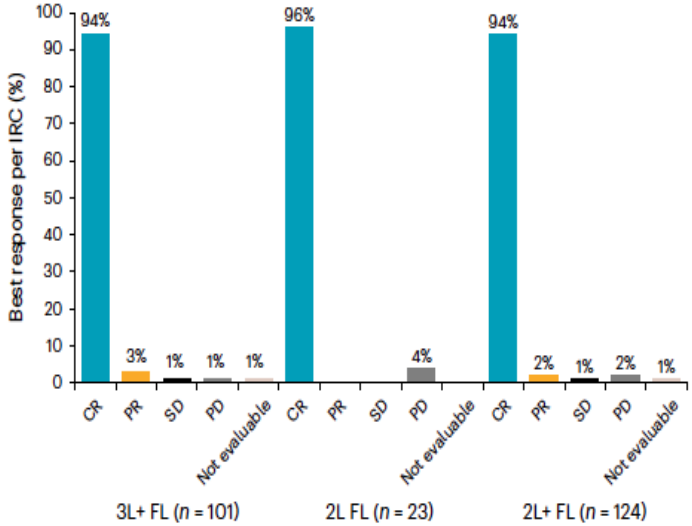

	ORR	CR rate
3L+ FL (*n* = 101)	97% (95% CI: 91.6–99.4) *P* < 0.0001[a]	94% (95% CI: 87.5–97.8) *P* < 0.0001[a]
2L FL (*n* = 23)	96% (95% CI: 78.1–99.9) *P* < 0.0001[b]	96% (95% CI: 78.1–99.9) *P* < 0.0001[b]
2L+ FL (*n* = 124)	97% (95% CI: 91.9–99.1)[c]	94% (95% CI: 88.7–97.7)[c]

	2L+ FL (*n* = 130)
CRS[a], *n* (%)	
Any grade	75 (58)
Grade 1	55 (42)
Grade 2	19 (15)
Grade 3[b]	1 (1)
Grade 4/5	0
Median time to first onset of CRS (range), d	6.0 (1–17)
Median time to resolution of first CRS (range), d	3.0 (1–10)
Treatment for CRS, *n* (%)	
Tocilizumab only	18 (14)
Corticosteroids only	0
Both tocilizumab and corticosteroid	15 (12)
Tocilizumab and/or corticosteroid	33 (25)
Vasopressors[c]	2 (2)
NEs[d], *n* (%)	
Any grade	20 (15)
Grade 1	15 (12)
Grade 2	2 (2)
Grade 3[e]	3 (2)
Grade 4/5	0
Median time to first onset of NE (range), d	8.5 (4-16)
Median time to resolution of first NE (range), d	3.5 (1-17)

Lisocabtagene maraleucel in follicular lymphoma: the phase 2 TRANSCEND FL study

Franck Morschhauser[1], Saurabh Dahiya[2,3], M. Lia Palomba[4], Alejandro Martin Garcia-Sanch
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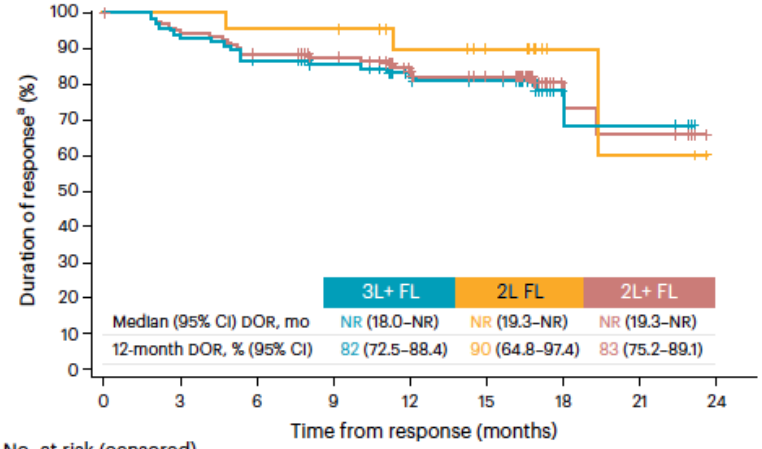
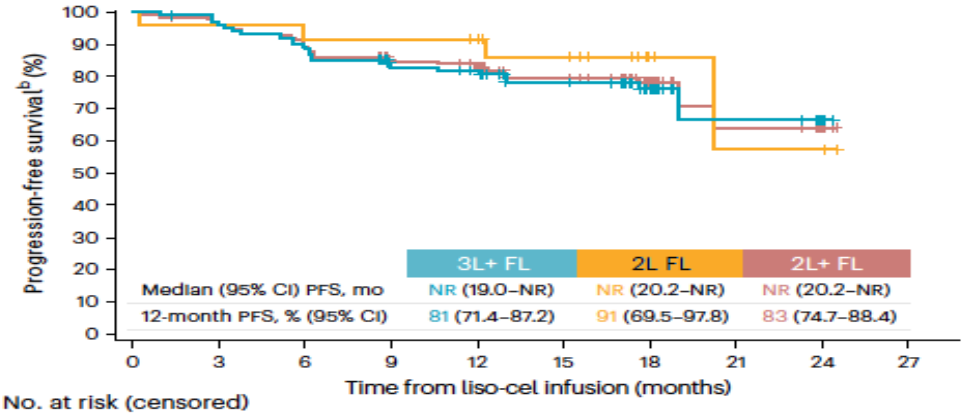


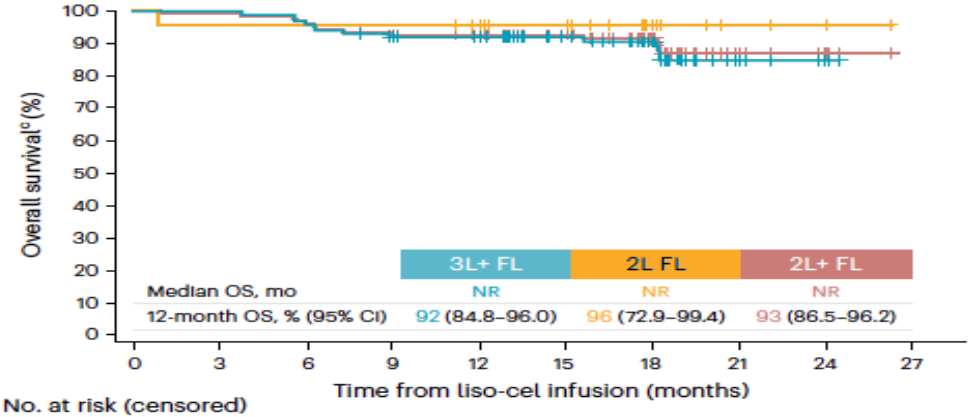
No. at risk (censored)

3L+ FL	98 (0)	91 (1)	83 (1)	77 (5)	62 (12)	49 (12)	8 (40)	7 (0)	0 (7)
2L FL	22 (0)	22 (0)	21 (0)	21 (0)	16 (4)	13 (3)	3 (10)	2 (0)	0 (2)
2L+ FL	120 (0)	113 (1)	104 (1)	98 (5)	78 (16)	62 (15)	11 (50)	9 (0)	0 (9)



No. at risk (censored)

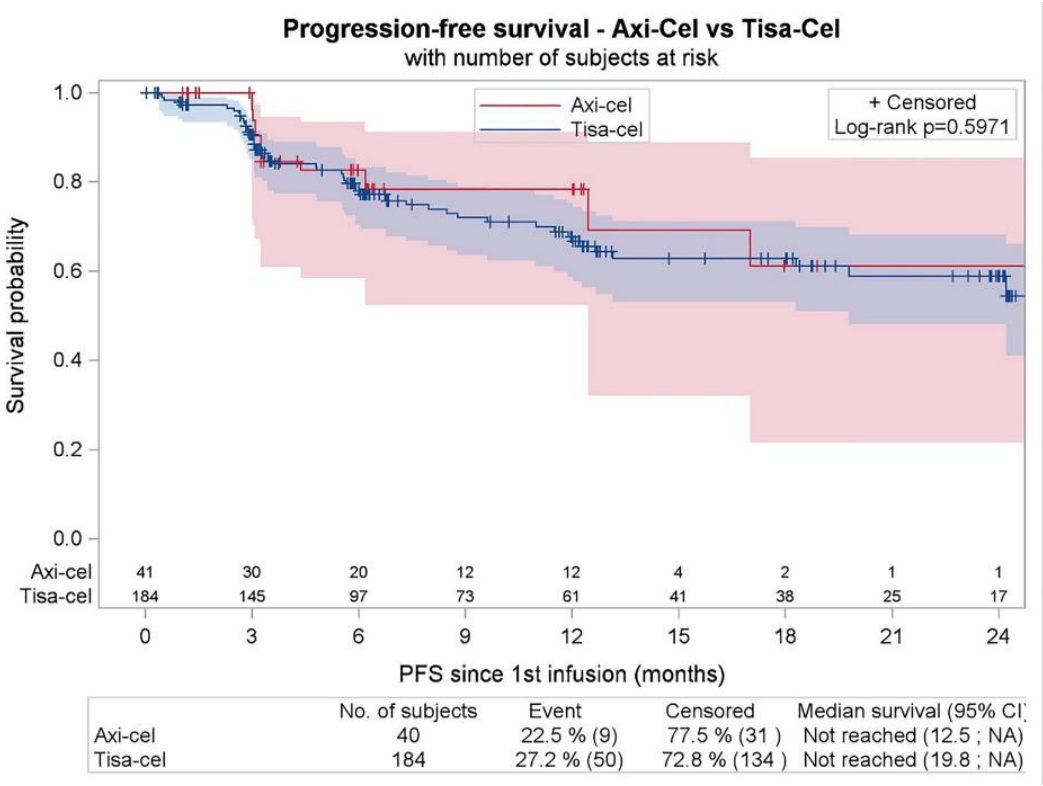
3L+ FL	101 (0)	96 (1)	89 (0)	78 (6)	72 (3)	50 (20)	19 (30)	7 (11)	2 (5)	0 (2)
2L FL	23 (0)	22 (0)	21 (0)	21 (0)	20 (1)	16 (3)	5 (11)	2 (2)	2 (0)	0 (2)
2L+ FL	124 (0)	118 (1)	110 (0)	99 (6)	92 (4)	66 (23)	24 (41)	9 (13)	4 (5)	0 (4)



No. at risk (censored)

3L+ FL	101 (0)	101 (0)	97 (0)	90 (3)	86 (4)	63 (23)	38 (24)	11 (25)	3 (8)	0 (3)
2L FL	23 (0)	22 (0)	22 (0)	22 (0)	20 (2)	17 (3)	8 (9)	3 (5)	2 (1)	0 (2)
2L+ FL	124 (0)	123 (0)	119 (0)	112 (3)	106 (6)	80 (26)	46 (33)	14 (30)	5 (9)	0 (5)

CAR-T in R/R FL: DESCART registry; 229 patients infused: tisa-cel (N = 187, 81.7%) or axi-cel (N = 42, 18.3%). Median follow-up: 7.1 months (95% CI: 6.3–12).



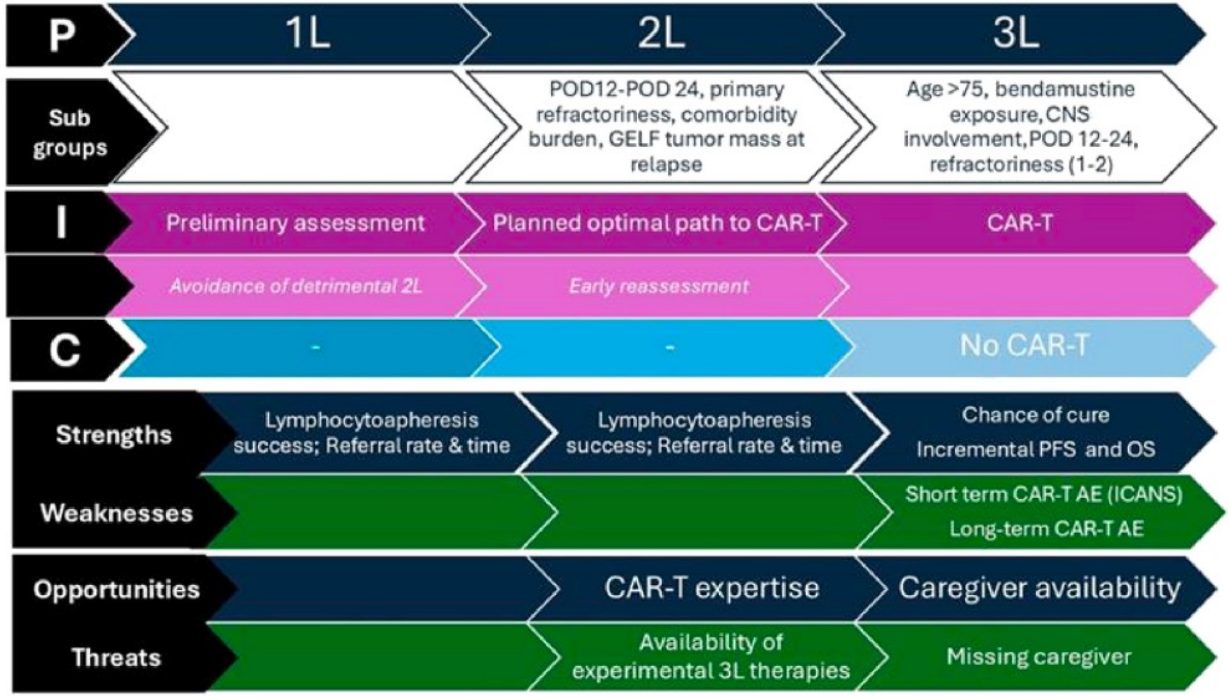
	No. of subjects	Event	Censored	Median survival (95% CI)
Axi-cel	40	22.5 % (9)	77.5 % (31)	Not reached (12.5 ; NA)
Tisa-cel	184	27.2 % (50)	72.8 % (134)	Not reached (19.8 ; NA)

Ysebaert L, Hematol Oncol 2025.

A SWOT-Consensus for CAR-T in Follicular Lymphoma: Fine Tuning of Patient Journey and Selection

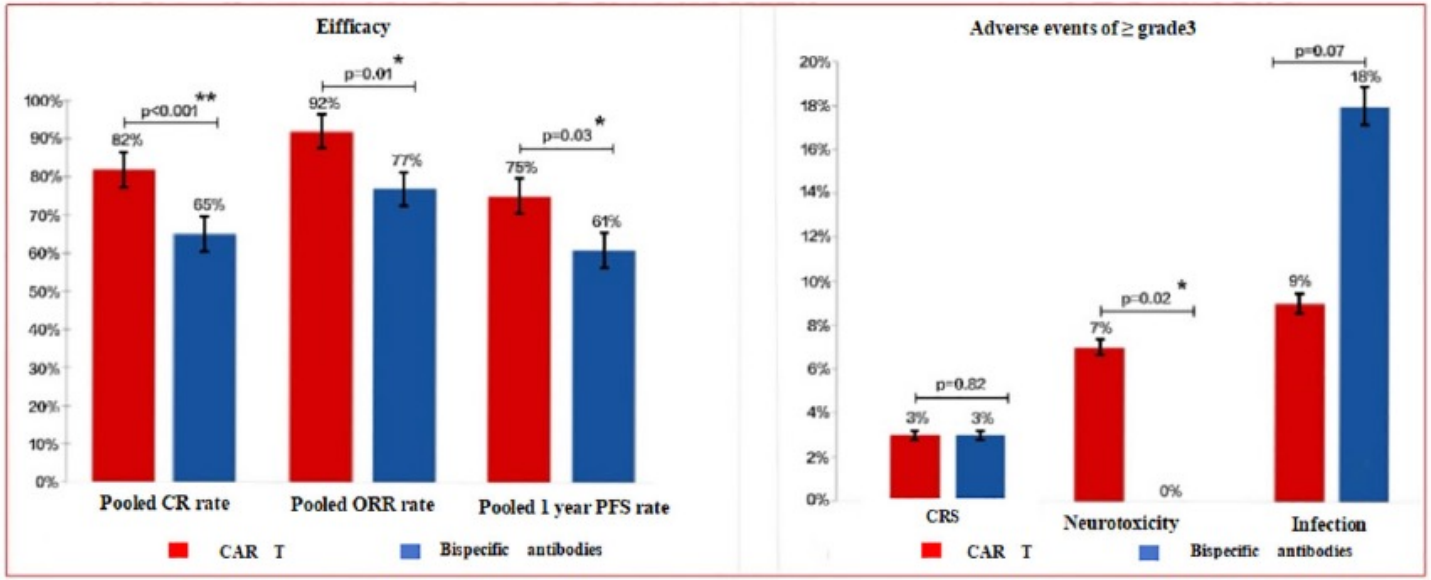
Monia Marchetti[1] | Paolo Corradini[2] | Luca Arcaini[3] | Stefania Bramanti[4] | Alice Di Rocco[5] | Marco Ladetto[6] | Stefano Luminari[7,8] | Luigi Rigacci[9] | Pier Luigi Zinzani[10,11]

Hematological Oncology, 2025; 43:e70125



CAR T-cells vs. bispecific antibodies as third- or later-line treatment for relapsed/refractory follicular lymphoma: a literature review and meta-analysis

CAR-T cell therapy: 6 studies including 376 patients
Bispecific antibodies: 6 studies including 505 patients



Conclusion: CAR-T cell therapy shows better efficacy than bispecific antibody in treating relapsed/refractory follicular lymphoma, but with higher severe neurotoxicity.

He Y et al, Front Immunol 2025.

Treatment of relapsed and refractory follicular lymphoma: which treatment for which patient for which line of therapy?

Carla Casulo[1] and Laurie H. Sehn[2]

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Treatment	Trial	ORR	PFS	OS
Tazemetostat (*EZH2* inhibitor)	E7438-G000-101 (phase 2)	35%, 67% in *EZH2*-mutant patients	Median, 13.8 months (overall), 19.2 months in *EZH2*-mutant group	NR
Lenalidomide and rituximab	AUGMENT (phase 3)	76%	Median, 39.4 months (R^2) vs 14.1 months (rituximab alone)	5-year, 83.2% (R^2 arm) vs 77.3% (placebo arm)
Tafasitamab + R^2	inMIND (phase 3)	83.5%	Median, 22.4 months	Median, NR
Lenalidomide + obinutuzumab	GALEN (phase 2)	70%	2-year, 65%	Median, NR
Zanubrutinib and obinutuzumab	ROSEWOOD (phase 2)	68%	Median, 28 months (ZO) vs 10.4 months (obinutuzumab)	At 24 months, 77% (ZO) vs 71% (obinutuzumab)
Mosenutuzumab (CD20×CD3 bispecific antibody)	GO29781 (phase 2)	~78%	Median, 14.3 months	3-year, 82%
Odronextamab (CD20×CD3 bispecific antibody)*	ELM-2 (phase 2)	80%	2-year, 46%	2-year, 70%
Epcoritamab (CD3×CD20 bispecific antibody)	EPCORE NHL-1 (phase 2)	82%	Median, 19.5 months (R/R FL)	1.5-year, 70%
Axi-cel (CAR T-cell therapy)	ZUMA-5 (phase 2)	92%	Median, 24.3 months (R/R FL)	Median, 87.3% at 24 months
Tisa-cel (CAR T-cell therapy)	ELARA (phase 2)	65%	Median, 14.8 months (R/R FL)	Median, 79% at 24 months
Liso-cel (CAR T-cell therapy)	TRANSCEND (phase 2)	73%	Median, 18.1 months	Median, NR

FOLLICULAR LYMPHOMA

Treatment of relapsed and refractory follicular lymphoma: which treatment for which patient for which line of therapy?

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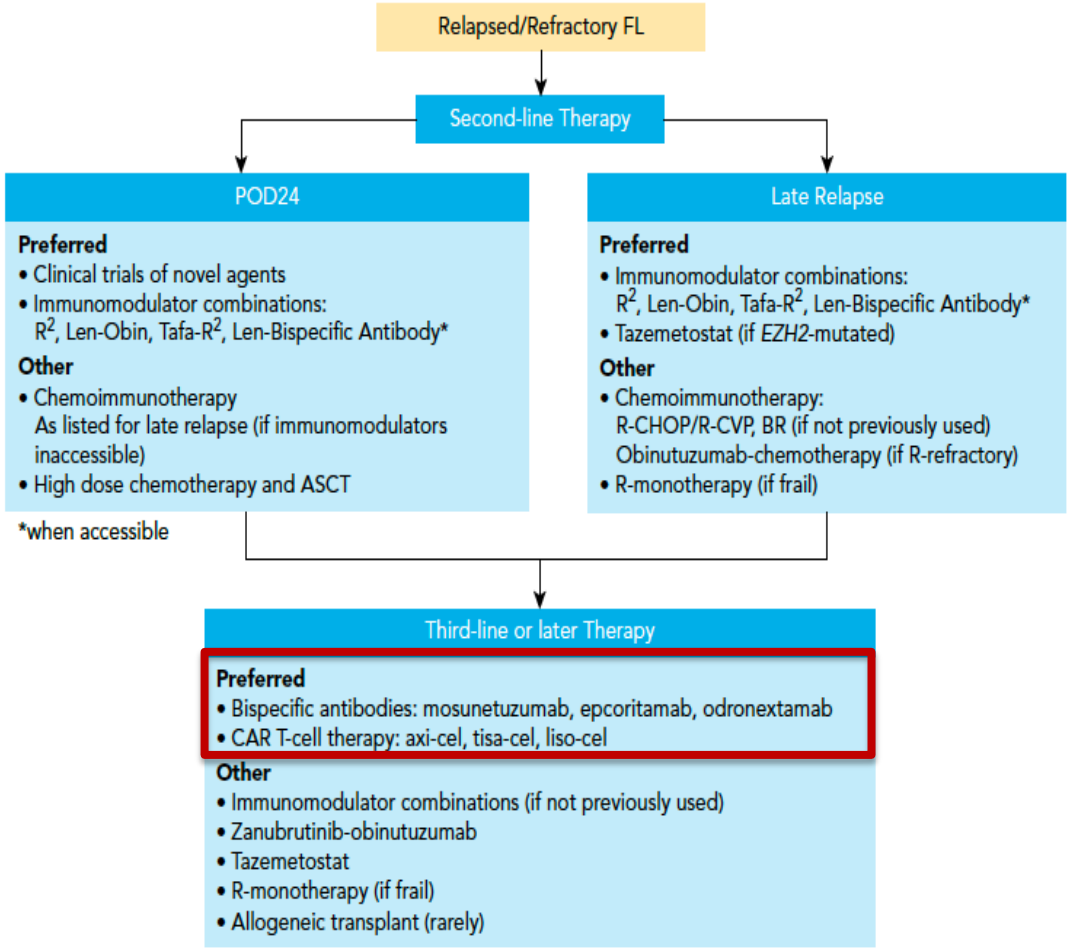
Considerations (at each relapse)
- Clinical trial participation
- Restaging:
  - Excisional biopsy to exclude transformation
  - Routine labs, including LDH and EZH2 mutation status (if indicated)
  - FDG-PET
  - BM bx (only if indicated)



Take home messages

- CD19 CAR-T therapy has achieved remarkable responses in relapsed/refractory B-NHL
- In R/R follicular lymphomas, axi-cel (ZUMA-5), tisa-cel (ELARA), liso-cel (TRANSCEND) confirmed durable responses and long-term survival benefit
- Lymphoma-specific PFS may more accurately represent the curative potential of CAR T-cell therapy in FL. This analysis showed a plateau in lymphoma-specific PFS emerging after 2 years, with only two events after month 30 in the ZUMA-5 study, at 5-years follow-up
- CAR T-cells seems more effective than BsAb based on higher CR and improved PFS, with similar rates of CRS and ICANS, in heavily pre-treated patients
- Enrollment in clinical trials and collection of real-life data is important

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All the Italian qualified centers for CAR-T treatment, the referral centers, patients, families and nurses.

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